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SYMPOSIA

Spindle Cell Lesions—Neoplastic or Non-Neoplastic?

Spindle Cell Carcinoma and Other Atypical Spindle Cell Lesions of the Head and Neck

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Abstract One challenging feature of head and neck pathology is that a dizzying array of spindle cell lesions occur here ranging all the way from reactive to malignant and very aggressive. This makes accurate diagnosis critical. At mucosal sites, the most important of these is spindle cell carcinoma (SpCC). Most SpCC are overtly malignant, and the differential diagnosis then includes a number of different malignant spindle cell neoplasms. However, there are several benign or even non-neoplastic lesions that can sometimes be difficult to discern from SpCC. The pathologic and clinical features can resolve this differential diagnosis. This review will focus on the clinical and diagnostic features of SpCC and the select non-neoplastic or benign lesions which are occasionally hard to distinguish from it.

Keywords Spindle cell carcinoma · Spindle cell lesions · Head and neck

Introduction

Spindle cell lesions of the head and neck are quite diverse with great clinical and biological heterogeneity. Some are malignant while many others are benign or simply reactive in nature. Spindle cell lesions can occur in head and neck skin, in the soft tissues of the scalp, orbit, and neck, and along the upper aerodigestive tract (UADT) mucosa. The most common spindle cell lesion presenting along the UADT mucosa is spindle cell carcinoma (SpCC), which has many unique and challenging clinical and pathologic features. The spindle cell or sarcomatoid component of this tumor can mimic numerous other reactive, benign, and malignant lesions (Table 1). This is what makes SpCC one of the most interesting and challenging of all head and neck tumors. While it is the most common malignant lesion to present here, this certainly does not mean that what is sitting on your microscope stage tomorrow morning is not a rare mucosal presentation of one of these other lesions. Keeping this in mind, this review will cover SpCC of the UADT, drawing particularly from five main clinicopathologic studies encompassing 326 cases [1–5], review several selected non-neoplastic and benign/low grade lesions that can mimic it, and finally discuss how to differentiate SpCC from them.

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Discussion

Spindle Cell Carcinoma

SpCC is a variant of squamous cell carcinoma which has spindled or pleomorphic tumor cells which simulate a true sarcoma but are epithelial in nature. For years, the true pathophysiology of this spindled component was debated, leading to numerous alternate terms, including carcinosarcoma, pseudosarcoma, pleomorphic carcinoma, and metaplastic carcinoma, among others [1]. Many different theories to explain the morphology were put forward in the past, including divergent differentiation of carcinoma cells, so-called "collision" tumors where there are two separate neoplastic clones combined in the same lesion, and the concept that squamous carcinoma "drives" the proliferation of a pseudosarcomatous stromal response. Over time, numerous studies analyzing the morphologic [2],

Table 1 Differential diagnosis for spindle cell lesions presenting at UADT mucosal sites

Malignant	Benign or low grade	Non-neoplastic
Spindle cell carcinoma[a]	Nodular fasciitis	Sinonasal polyp with stromal atypia[a]
Spindle cell melanoma	Glomangiopericytoma	Ulcer with granulation tissue/ radiation-induced atypia[a]
Spindle cell myoepithelioma or carcinoma	Inflammatory myofibroblastic tumor[a]	Vocal cord nodule with stromal atypia[a]
Kaposi's sarcoma	Solitary fibrous tumor	Contact ulcer[a]
Other sarcomas: angiosarcoma, synovial sarcoma, MPNST	Ossifying and non-ossifying fibroma	Giant cell fibroma

[a] Lesions covered in this review. MPNST, malignant peripheral nerve sheath tumor

immunohistochemical [1, 3, 5–8], ultrastructural [8], and molecular [9] features of SpCC have shown epithelial characteristics in the spindle cell population as well as marked genetic similarity between the spindled and squamous portions of biphasic tumors, clearly indicating that the spindle cell component represents divergent differentiation by what is a true carcinoma. Most SpCC are biphasic tumors. In other words, they are composed of both a conventional squamous cell carcinoma and a spindle cell or pleomorphic component [1, 7, 8]. However, as many as one-third are monophasic spindled or pleomorphic tumors making the diagnosis of carcinoma more difficult.

SpCC has the same demographics as conventional squamous cell carcinoma, occurring primarily in the fifth and sixth decades, being strongly associated with smoking and drinking, and showing a strong male preponderance [1, 2, 4–7]. The larynx, particularly the glottis, is the most common primary site followed by the oral cavity, specifically the tongue, floor of mouth, and gingivae. Less common sites are the hypopharynx, oropharynx, sinuses, and nasal cavity [4, 6, 7]. A significant minority of patients have a history of previous radiation to the originating site. Combining five major SpCC clinicopathologic studies, 18% of the 326 cases occurred in a previously irradiated field at an average of 7 years and as late as 16 years later [1–5]. This compares with a rate of only 1% or less for conventional squamous cell carcinoma. Of note, none of the cases of SpCC arose less than 1 year after radiation. Tumors of the larynx present with rather typical symptoms such as hoarseness, voice change, dyspnea, stridor, and cough [1]. Tumors of the oral cavity and oropharynx typically present with just the complaint of a mass or with swelling, pain, a non-healing ulcer, dysphagia, or bleeding [2].

A unique clinical and pathologic feature of SpCC is its macroscopic growth pattern. Greater than 90% of laryngeal and pharyngeal tumors present as polypoid and exophytic masses projecting into the lumen [1, 3, 5]. The average size of laryngeal tumors is approximately 2 cm, but lesions as small as 2 mm have been reported [1, 5]. In the oral cavity, the growth pattern is somewhat more variable with 50–60% of tumors being exophytic [2]. The average size of the tumors is 2 cm with lesions as small as 0.6 cm reported [2, 4]. The exophytic masses are usually smooth, dark brown, and lobulated with extensive mucosal ulceration. As previously mentioned, most SpCC are biphasic tumors with areas of conventional squamous cell carcinoma admixed with areas of spindled and/or pleomorphic tumor [1, 5, 7]. In the Thompson et al. study of laryngeal SpCC from the Armed Forces Institute of Pathology, they performed extensive H&E leveling of cases sent to them in consultation looking keenly for a conventional squamous component. It was identified in 80% of cases [1]. Other studies have ranged from 60% to 90% [1, 3, 5, 7, 8]. The spindled component usually predominates. The squamous component can be either focal dysplasia, carcinoma in situ, or frankly invasive squamous cell carcinoma. This latter component is usually present in the stalk of the polyp, at the deepest aspect or advancing front of the tumor. When dysplastic squamous epithelium remains on the surface, the spindle cells frequently can be seen "dropping off" from its basal layer [1, 2] (Fig. 1a). Surface squamous neoplasia is probably lost in many cases due to the extensive surface ulceration which is typically present.

The spindled cells may be bland and regular (Fig. 1b) or may be markedly pleomorphic with multinucleated giant tumor cells (Fig. 1a). There may be a wide variety of architectural patterns including fascicular, storeiform, lace-like, or myxoid and on occasion, truly definable sarcomatous differentiation, such as osteosarcomatous, chrondrosarcomatous, or rhabdomyosarcomatous, may be seen [1, 2, 4–6, 8]. Typically, the spindle cell component is more haphazard than most true sarcomas, with any fascicle formation limited and irregular. Sometimes, "transition-type" cells with a morphology in-between the carcinoma and spindled component are seen. These cells are epithelioid but not nested. Some SpCC will present as extensively ulcerated masses with tumor cells widely spaced apart in a loose, pale or myxoid background. There are frequently abundant small vessels with plump endothelial cells and numerous inflammatory cells, particularly neutrophils (Fig. 1c). These SpCC can closely mimick exuberant granulation tissue (a major

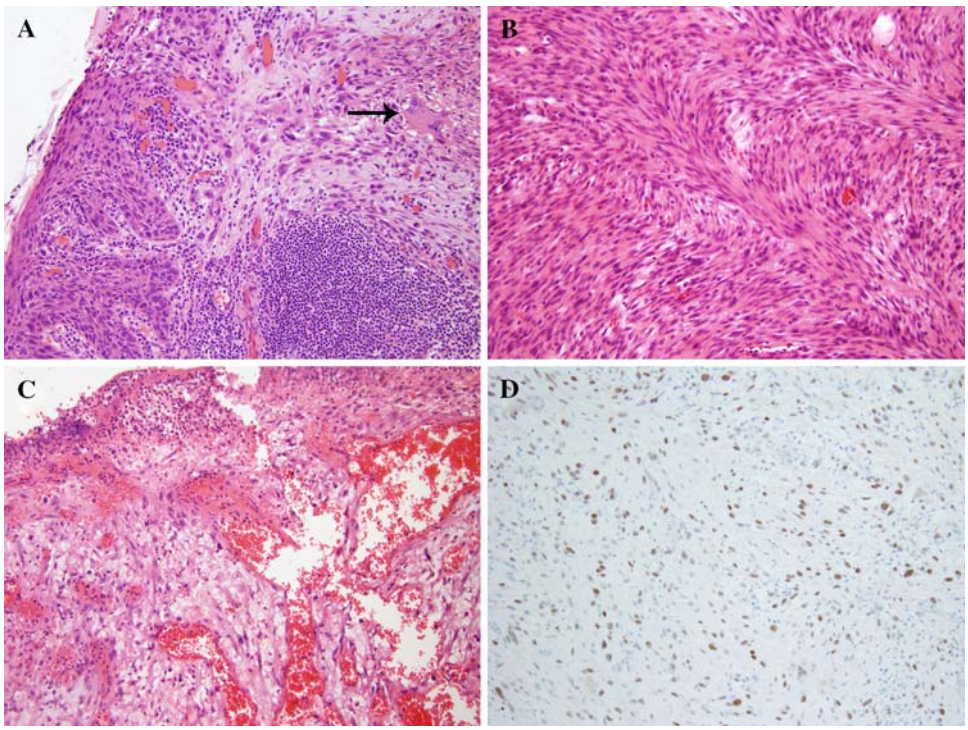

Fig. 1 Histology of spindle cell carcinomas. (**a**) Spindled and pleomorphic tumor cells "dropping off" from squamous cell carcinoma in situ (200×); arrow indicates a tumor giant cell; (**b**) cellular spindle cell component of a spindle cell carcinoma with fascicles of relatively regular cells with fusiform nuclei (200×); (**c**) spindle cell carcinoma mimicking inflamed granulation tissue with an ulcerated surface, irregular and atypical cells widely spaced in a loose stroma, and abundant small vessels and inflammatory cells (200×); (**d**) p63 immunohistochemistry showing strong nuclear staining of tumor cells from the lesion in panel C (200×)

pitfall for the surgical pathologist), particularly on frozen section. Finally, another pitfall is where the spindle cell component demonstrates loss of cohesion of the tumor cells and consequently mimics an angiosarcoma. This has been described in other body sites as pseudoangiosarcomatous carcinoma and has also been reported in oral cavity SpCC [10]. Mitotic activity can vary, but averages more than one per high power field with a range from 0 to over 10. Atypical mitoses are common (seen in ~75% of cases) [1].

Immunohistochemistry has been extensively analyzed in SpCC (Table 2). Obviously key to the diagnosis is the confirmation of epithelial differentiation in the spindle cells. Most, but unfortunately not all, cases of SpCC will show staining for one or more epithelial markers. The most commonly used keratin stain, AE1/AE3 or pancytokeratin, is reported to be positive in between 26% and 62% of cases [1, 5, 7, 8, 11]. Epithelial membrane antigen (EMA) staining is reported to be positive in between 4% and 47% of cases [1, 5–7]. An additional epithelial marker, p63, was positive in 63% of 19 cases of SpCC [5] (Fig. 1d). When exhaustive keratin staining was combined with EMA staining on laryngeal SpCC, Thompson et al. found that the spindle cell component was positive for at least one epithelial marker in only 68% of cases [1]. With combined pancytokeratin (AE1/AE3 + CAM 5.2), EMA, and p63 staining, only 79% of cases were positive for at least one of them [7]. These numbers are not significantly different for cases with a clearly-identifiable mixed component of squamous neoplasia and for those without. This leaves a significant minority of cases where there is no definitive light or immunohistochemical evidence of epithelial differentiation. SpCC has been shown to be positive for mesenchymal-type markers as well. Virtually 100% of cases are positive for vimentin [1, 5, 8, 11] and a significant minority for smooth muscle actin (31–33%) and muscle specific actin (15–42%) [1, 11].

Given the unique growth pattern and the wide morphologic variation that is possible in SpCC, the differential diagnosis is a long one. The features of several non-neoplastic and benign or low grade lesions in this differential will be discussed, and then the overall picture and the features and studies used to arrive at a diagnosis will be addressed.

Granulation Tissue, Polyps, and Contact Ulcers

Inflamed granulation tissue can be clinically and histologically concerning for malignancy. This is particularly true in cancer patients after radiation therapy [12]. The pathologist sees many such biopsies in daily practice. Because of the heterogeneity of the clinical scenarios here, these lesions can be seen anywhere along the UADT. There are also specific clinical lesions, such as the laryngeal contact ulcer or so-called "granuloma", that consist of inflamed granulation tissue [13]. These are frequently seen in patients after intubation, with ongoing, severe gastroesophageal reflux disease (GERD), or with a history of overuse of their voice [14]. They are almost always on the posterior true cord or vocal process of the arytenoids [14, 15] but rarely can be seen on other parts of the true cord [13].

Table 2 Immunohistochemistry in the sarcomatoid component of spindle cell carcinoma

	Thompson et al. [1]—larynx	Lewis et al. [5]—larynx	Ellis et al. [6]—all sites	Zarbo et al. [8]—all sites	Nakhleh et al. [11]—all sites	Lewis et al. [7]—all sites
Pancytokeratin (AE1/AE3 ± CAM 5.2)	32/123	12/26	13/21	7/16	12/24	5/17
	26%	46%	62%	44%	50%	29%
EMA	21/117	1/26	4/21	NP	NP	9/19
	18%	4%	19%			47%
p63	NP	NP	NP	NP	NP	12/19
						63%
Any epithelial marker[a]	68%	65%	81%	48%	50%	79%

[a] Variable panels of cytokeratins utilized; NP, not performed

Clinically, the concerning tissue is at the edges of a heaped-up ulcer or sometimes can be exophytic and mass-forming with a smooth surface [15, 16]. These are usually granular and friable. Contact ulcers occur on the posterior true cords [16] and are bilateral in approximately 5% of cases. They can be as large as 3 cm [13] and usually are smooth surfaced and pink-tan. Histologically, all of these lesions have a similar appearance. There is an extensively ulcerated surface covered by fibrinopurulent material (Fig. 2). The core of the tissue is made up of numerous small vessels with plump endothelial cells. The stroma around them is loose or edematous and occasionally quite myxoid. Within it are stellate and plump myofibroblasts and endothelial cells with tapered processes and round to oval nuclei, frequently with open chromatin and small nucleoli (Fig. 2 inset). The nuclei are not densely hyperchromatic. There may be multinucleation and mitotic figures are scattered but not overly prominent (rarely ever more than one per high power field). With extremely rare exception, there should be no atypical mitoses [12]. There are also intermixed inflammatory cells, frequently consisting of a rich collection of neutrophils, plasma cells, and lymphocytes. The neutrophils are particularly prominent in the superficial aspects under the ulcerated surface. In longstanding contact ulcers, a prominent and more cellular fibrosis may develop [14]. In post-radiation ulcers, there may be extreme cytologic atypia, but this is uncommon [12]. All of the fibroblasts and endothelial cells are negative by immunohistochemistry for cytokeratins [7, 12] and p63 [7].

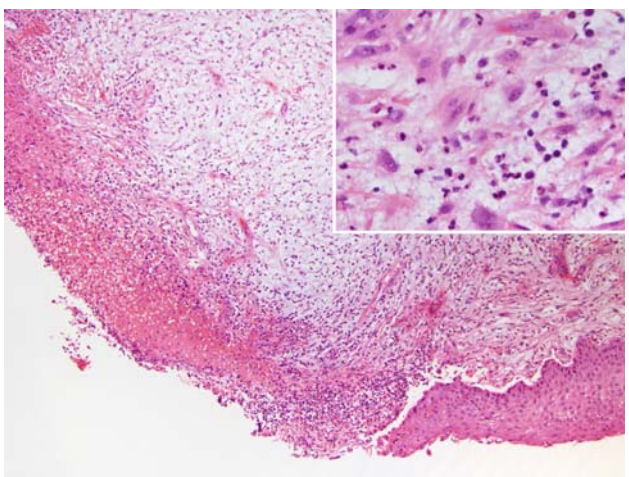

Fig. 2 Inflamed granulation tissue with an ulcerated surface and stellate, atypical stromal cells (inset) with round to oval nuclei, some with prominent nucleoli (100×; inset 400×)

Granulation tissue will resolve with the associated lesion over time. Contact ulcers will only resolve once the inciting cause is removed. If GERD is responsible, this must be treated. Surgical pathologists are good at recognizing the lesions as inflamed granulation tissue, but must be aware of contact ulcers as a specific entity to remind the clinician to treat any underlying cause [13, 15].

Vocal Cord Nodule with Stromal Atypia

This peculiar phenomenon is described in only a few reports in the literature. The vocal cord nodule (VCN) (or polyp) is a specific and quite common [17] lesion seen on the true cord at the junction of the anterior one-third and posterior two-thirds. In the reverse of almost all other UADT mucosal lesions, VCN is much more common in women and is related to vocal abuse. Clinically, patients present with hoarseness and on laryngoscopy, the lesions are smooth, nodular, rounded, gray–yellow, and somewhat translucent [16]. Most measure only a few millimeters.

Microscopically, VCN can be of four different types based on the stromal constituents: (1) myxoid (2) fibrinous (3) vascular (4) fibrous. There is often a mixture of different patterns [18]. The stroma is loose and, for the myxoid and fibrous types, has widely scattered, bland spindle cells. The vascular type has numerous small vessels in the stroma with some hemorrhage, and the fibrinous type has large lakes of extracellular, eosinophilic fibrin. The surface squamous epithelium is almost always intact (ulceration is quite uncommon) and may be completely normal or slightly hyperkeratotic.

Rare VCN may have atypical stromal cells that simulate malignancy [16, 19]. These lesions have been described as clinically and macroscopically identical to typical VCN. Microscopically, there is a moderately cellular (Fig. 3) component of atypical fibroblasts which have relatively open chromatin and may have small nucleoli. In the reported cases, the background stroma has been myxoid and the surface mucosa intact, just as in typical VCN. There is no confluent cellularity, no collection of the cells beneath the epithelium to simulate a "cambium layer," and virtually no mitotic activity [16]. The atypia is usually moderate in degree. Severe atypia has been reported in a single case report of a 1.5 cm myxoid mass on the true cord. It was excised endoscopically, and the patient was free of disease after 2 years of follow-up. However, he was an 80-year-old male smoker and nothing clearly distinguished this lesion from a small SpCC [19].

VCN with stromal atypia has not been noted to behave any different clinically than typical VCN. Excision is curative [16].

Sinonasal Polyp with Stromal Atypia

Sinonasal inflammatory polyps (IP) are a common and easily diagnosable part of head and neck pathology. However, rare cases can have stromal cells with marked cytologic atypia and thus mimic true neoplasms such as a neurofibroma [20–22] or embryonal rhabdomyosarcoma. Other tumors such as SpCC, in theory, can appear similar given the polypoid growth, occasional ulceration, and marked inflammation.

Typical IP are associated with long-standing rhinitis and allergy symptoms. They are non-neoplastic outpouchings of sinonasal mucosa with thickened, hyalinized basement membranes and a loose, edematous stroma with widely scattered fibroblasts and abundant mixed inflammatory cells, particularly eosinophils. Rare cases have marked cytologic atypia in the stromal fibroblasts [20–22]. These patients have had the typical clinical history of chronic rhinosinusitis and have ranged in age from 4 to 47 years (average between 14 and 26 years) [21, 22] making them essentially no different than for typical IP.

Clinically and grossly, they have the usual appearance of IP with a glistening gray–yellow color and translucency and average size of 2–4 cm. Microscopically, they have a loose, edematous stroma with abundant mixed chronic inflammatory cells. There may be hemorrhage and thrombosed vessels (so-called "angiomatous" features). There are areas with mildly increased cellularity (Fig. 4). Scattered throughout, but particularly in these areas, are markedly atypical stromal cells with large, hyperchromatic nuclei, some with large, distinct nucleoli. They do not coalesce into cellular masses or collections, however, and there is no mitotic activity. Also, importantly, there is no subepithelial condensation that might mimic a "cambium layer" like that seen in a botyroid rhabdomyosarcoma [21, 22]. The surface epithelium is typically respiratory and completely intact [22]. However, it may be ulcerated or show squamous metaplasia. One study has examined immunohistochemistry of IP with stromal atypia [21]. In all 29 cases, the atypical cells were positive for vimentin. Sixty-two percent of cases were positive for smooth muscle actin, 48% for muscle specific actin, and, surprisingly, 76% for pancytokeratin (AE1/AE3 + CK1). The cells are negative for desmin, myoglobin, GFAP, and S-100. In this thorough analysis which also included electron microscopy, the authors concluded that these cells are reactive myofibroblasts [21].

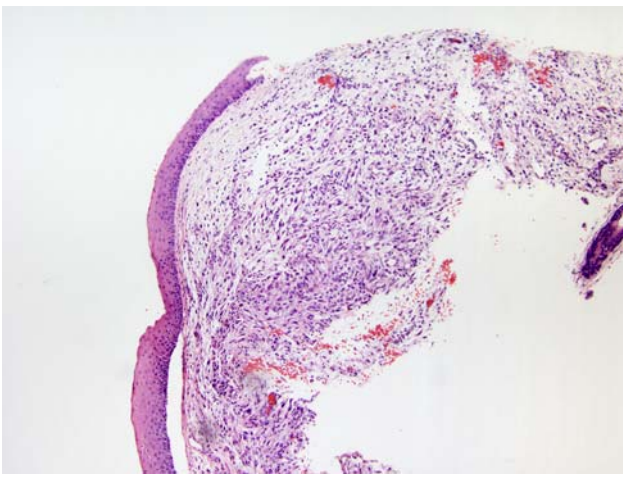

Fig. 3 Vocal cord nodule with stromal atypia demonstrating an intact and unremarkable surface squamous mucosa and a moderately dense collection of atypical spindle cells in the submucosa (40×)

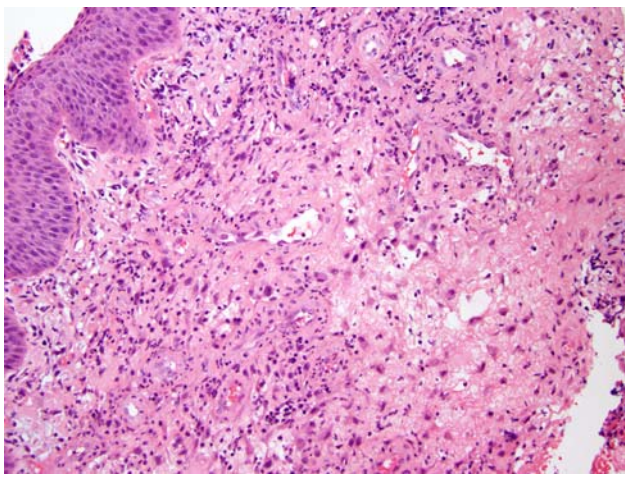

Fig. 4 Widely scattered atypical stromal cells in the submucosa of an inflammatory polyp with atypical stromal cells. The stroma in between the stromal cells is loose and edematous with chronic inflammatory cells, and the surface mucosa shows squamous metaplasia (200×)

On long-term clinical follow-up, no patient has had clinically malignant disease. Polyps have recurred in a subset, but these are again removed, and the patients are otherwise fine [21, 22].

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is a curious low grade tumor consisting of a proliferation of myofibroblastic cells with a variable admixture of inflammatory cells [23]. It was previously thought to be reactive in nature, but recent studies have conclusively proven most cases to be neoplastic. Alternative terms include plasma cell granuloma and inflammatory pseudotumor [23]. They have been reported in myriad sites but are most common in the soft tissue and viscera (particularly the lung) over a very broad age range but predominantly in children and young adults. The head and neck is a relatively uncommon site, particularly if one considers mucosal-based lesions. There are 19 reported cases in the larynx [23, 24], making it the most common head and neck site. Other reported sites include the oral cavity, nasal cavity and paranasal sinuses, and tonsil. IMT has not been reported in the nasopharynx. In head and neck IMT, patients are usually adults, particularly for laryngeal cases [23], and although many IMT patients present with constitutional symptoms, this is also uncommon in head and neck cases.

Clinically, IMT presents similarly to other lesions at the given sites, with hoarseness and stridor in the laryngeal cases [23]. It is typically exophytic or nodular with smooth masses projecting into the lumen. Histologically, the mucosal surface may be intact, hyperplastic, or ulcerated but without dysplasia. Laryngeal lesions, in particular, are usually polypoid [23]. IMT consists of a submucosal proliferation of spindled to stellate cells arranged in poorly formed fascicles or in a storeiform pattern. The cells can have very long cytoplasmic extensions which has been termed "spider-like" [23]. The cellularity is moderately high, but overall loosely organized (Fig. 5). The cells are typically plump but not markedly atypical. There is modest mitotic activity (rarely ever more than 3–4 per hpf) but atypical mitoses are never seen [23]. The stroma is highly vascular and ranges from edematous to myxoid to hyalinized. There is abundant associated inflammation, consisting predominantly of plasma cells but also with lymphocytes and eosinophils [23]. Immunohistochemistry is positive for vimentin, smooth muscle actin, and muscle specific actin in the spindle cells in all cases, with the actin staining ranging from diffuse to focal [23, 25]. Immunohistochemistry for cytokeratin is usually negative but has been reported to be focally positive in up to 60% of cases when using AE1/AE3 [25]. Although approximately 60% of all IMT are positive for the ALK-1 kinase, in the head and neck, almost all are negative [23].

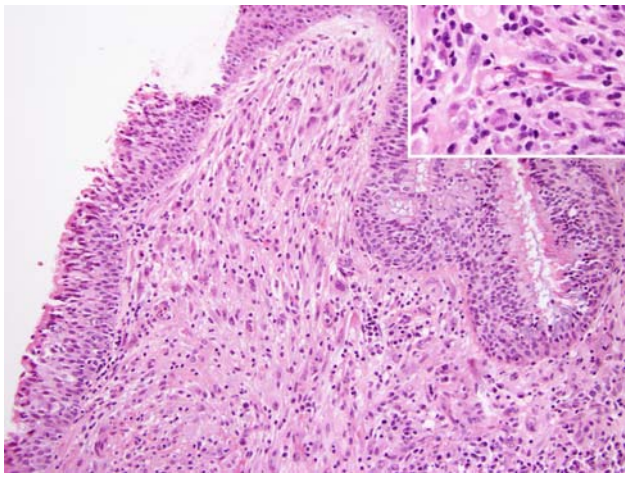

Fig. 5 Inflammatory myofibroblastic tumor of the larynx with a moderately dense spindle cell proliferation in the submucosa with prominent associated chronic inflammation rich in plasma cells. The atypical cells (inset) have large nuclei with vesicular chromatin and prominent nucleoli (200×; inset 400×)

Most IMT pursue a benign clinical course. Patients undergo conservative resection or can also be treated with corticosteroids or non-steroidal anti-inflammatory drugs. Approximately 25% will recur locally and, although rare, IMT has metastasized. However, this has never been demonstrated in head and neck cases.

Differential Diagnosis of Mucosal Spindle Cell Lesions

The majority of spindle cell lesions presenting at UADT mucosal sites are straightforward to diagnose. However, there are some lesions that are quite difficult to classify. With a keen eye to the H&E morphology, attention to the clinical scenario, and judicious use of immunostains (Table 3), one can work through these difficult cases.

There are not many "absolutes" among these lesions, but there are several important points that strongly favor malignancy. Finding true squamous neoplasia (carcinoma in situ or invasive squamous cell carcinoma) blending with the lesion confirms SpCC. Obtaining deeper levels on small biopsies may be helpful to identify this. If the spindle cell lesion shows invasive growth at the periphery, has areas of dense cellularity, well-formed fascicles, or a dense collagenous background, these argue very strongly for malignancy. Individual cell features such as marked atypia in more than just scattered cells or marked nuclear hyperchromasia strongly suggest malignancy. Finally, atypical mitoses, with only the rarest of exceptions [12] are not seen in benign lesions.

Features that are almost always indicative of a non-neoplastic or benign lesion include zonation or true organization, particularly of vessels in the lesion, only widely

Table 3 Immunohistochemistry in UADT spindle cell lesions

	Cytokeratins	EMA	p63	SMA	MSA	Vimentin
SpCC	+	+	++	+/−	+/−	+++
VCN with stromal atypia	ND	ND	ND	ND	ND	ND
IP with stromal atypia	+	ND	ND	+	+	+++
Atypical GT and contact ulcer	−	−	−	ND	ND	+++
IMT	−/+	−/+	ND	+++	+++	+++

−, negative; −/+, rarely/focally positive; +/−, sometimes positive; +, positive in many cases; ++, positive in most cases; +++, consistently positive; ND, no data available; SpCC, spindle cell carcinoma; VCN, vocal cord nodule; IP, inflammatory polyp; GT, granulation tissue; IMT, inflammatory myofibroblastic tumor

scattered nuclear atypia, lesional cells consistently having only vesicular chromatin with small nucleoli, and lack of mitotic activity. Only very rare SpCC will completely lack mitotic activity [1].

SpCC can be distinguished from benign, reactive granulation tissue and/or contact ulcers based on several features. The clinical scenario for granulation tissue will usually be short term (days to weeks), after treatment of some kind, such as surgery, radiation therapy, or associated with mucosal trauma. Although granulation tissue can be mass-like or polypoid, it should never be more than a 2–3 cm and will not grow rapidly. SpCC either presents as a very rapidly growing mass or, alternatively, has a longer clinical history (weeks to months). It is usually larger than a few centimeters and is common in patients with a history of radiation for other malignancies [1, 2]. Whereas most granulation tissue lesions occur within weeks to months of radiation treatment, SpCC is almost always more than 1 year, and usually many years, later. On histology, the nuclei of reactive granulation tissue tend to have more open chromatin and sometimes small nucleoli. Although there is some degree of pleomorphism, it is rarely profound. SpCC nuclei, on the other hand, has hyperchromatic nuclei with much more pleomorphism. Although SpCC can be quite hypocellular, one can usually find at least focal areas of more confluent cellularity. Most SpCC will have some foci of clear squamous differentiation. Granulation tissue will have modest mitotic activity, but will almost never have more than one per high power field and will not have atypical mitoses. By contrast, SpCC usually has brisk mitotic activity and has atypical mitoses in $\sim$75% of cases. The one glaring exception to the histologic distinction is a report of two cases of radiation-induced bizarre granulation tissue by Weidner et al. [12] where they describe ulcerated, tumefactive lesions of the postcricoid hypopharynx and right maxillary sinus. Both perfectly mimicked SpCC morphologically including very brisk mitotic activity, atypical mitoses, and no squamous neoplastic component. These lesions were negative for cytokeratin by immunohistochemistry. However, since not all cases of SpCC have a squamous component or pancytokeratin reactivity, the true nature of these two lesions is not entirely clear. Immunohistochemistry for epithelial markers is consistently negative in granulation tissue [7] and will be positive in approximately 70% of SpCC, specifically pancytokeratin and/or p63.

VCNs with stromal atypia can be concerning histologically, but they will be myxoid, will be moderately cellular without inflammation, will almost always have an intact surface epithelium, and will have no mitotic activity. SpCC is typically highly mitotically active with atypical forms. Immunohistochemistry for epithelial markers, although never actually performed and reported in the literature, would be expected to be negative in the spindle cells of VCN, as well. Sinonasal polyps (IP) with stromal atypia also can be concerning histologically, but they never reach a significantly dense cellularity and have no mitotic activity. Surface ulceration is uncommon in IP and virtually always present in SpCC. Interestingly, keratin immunohistochemistry is not discriminatory, being positive in the spindle cells of both lesions. The distinction lies squarely on histology, macroscopy, and clinical features.

IMT can be very difficult to distinguish from SpCC, occurring as exophytic, ulcerated, atypical spindle cell lesions projecting into the lumen of the UADT. Both lesions can be positive for cytokeratins as well (Table 3), although it is usually quite focal in IMT. The distinction lies in the absence of invasive growth, absence of markedly atypical cytologic features, and lack of atypical mitotic figures in IMT [23]. In addition, although SpCC can have an associated chronic inflammatory infiltrate, it is rarely rich in plasma cells while this is a characteristic feature of IMT. Immunostains for smooth muscle actin and muscle specific actin are typically strongly and diffusely positive in IMT. Immunostaining for ALK-1 is negative in most head and neck IMT so is not helpful.

Conclusion

There are numerous atypical spindle cell lesions which can present along the UADT mucosa. Because it is so common,

SpCC should be strongly considered and ruled out before diagnosing one of the less common lesions. With attention to the clinical scenario, careful evaluation the H&E morphologic features, and judicious use of immunostains, one can work through these difficult cases to arrive at the correct diagnosis.

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